Department Chemistry

Subject DR. PINNEY'S- RESEARCH

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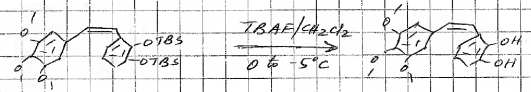
# DEPROTECTION USING TBAF

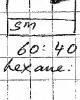
07/09/02




| MF | SM | TBAF in 1M THF | $CH_2Cl_2$ dry solvent |
|---|---|---|---|
| MW | 530.84 | 261.47 | |
| Ratio | 1 | 2.5 | |
| wt(g) | 2.02 | 2.49 (9.53ml) | |
| mmoles | 3.81 | 9.53 | |

PROCEDURE:

1. Dried the compound on pump for ½ hour.
2. Put under Ar.
3. Dissolve in $CH_2Cl_2$
4. Maintain temperature at -5°C by using ice bath to which NaCl is added.
5. TLC was done after 15min, 20, 25, 30, 35 min
6. Reaction was stopped after 35 min by quenching with $H_2O$.




60:40
hexane: EtOAc.

7. Transferred to a separatory funnel and added more $H_2O$ and do partitioning.

8. Collect the lower organic layer
9. Extract the aqueous layer with $CH_2Cl_2$ twice
10. The combined organic layers were dried with anhydrous $Na_2SO_4$
11. Filtered & rotavaped.

COLUMN CHROMATOGRAPHY 07/05/02

Did a column to collect purified diol

Used 70:30 hexane : EtOAc

Wt of diol collected = 0.5 g.

NMR

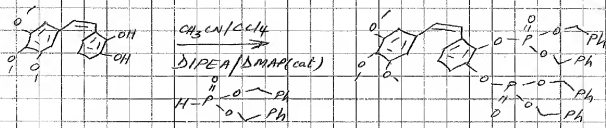
$^1H$ NMR PA-11-56

$^{13}C$ NMR PA-11-57


$$\text{Yield \%} = \frac{0.5}{302.32} = 1.66 \text{ mmoles}$$

$$\frac{1.66}{3.81} \times 100 = 43.40\%$$

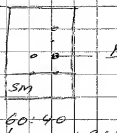
# DIBENZYL PHOSPHORYLATION OF DIOL 07/06/02




| MF | SM | $CCl_4$ | DIPEA | DMAP | DBP | $KH_2PO_4$ (0.5M) | $CH_3CN$ |
|---|---|---|---|---|---|---|---|
| MW | 302 | 153.82 | 129.24 | 122.17 | 262.25 | 136.09 | |
| wt(g) | 0.5(g) | 2.53(1.6ml) | 0.89(1.21ml) | 0.04 | 1.26(1.06) | | 10ml |
| Ratio | 1eq | 10eq | 4.2eq | 0.2eq | 2.9eq | | |
| mmoles | 1.65 | 16.5 | 6.95 | 0.33 | 4.8 | | |

PROCEDURE Ref Petit Antineoplastic agents 42.9 pg 207.

1. The diphenol was put Ar, cool to -20°C
2. Add $CH_3CN$, then add $CCl_4$ and stir for 10 min
3. Diisopropylethylamine and DMAP were then added.
4. 1 minute later dibenzyl phosphite was added and temperature was maintained below -20°
5. After 45 min do TLC to check completion formation




6. Then $KH_2PO_4$ (0.5M) was added and the

7. It was extracted with EtOAc, 4 times then washed with saturated NaCl and water and dried with anhydrous NaCl
8. It was rotavaped and the yellowish brown mixture was separated by column chromatography

COLUMN CHROMATOGRAPHY

Separated by flash chromatography using 70:30 hexane : EtOAc

Then use 60:40 hexane : EtOAc

Colourless oily liquid wt = 0.71 g

$^1H$ NMR PA-II-58

$^{31}P$ NMR PA-II-59

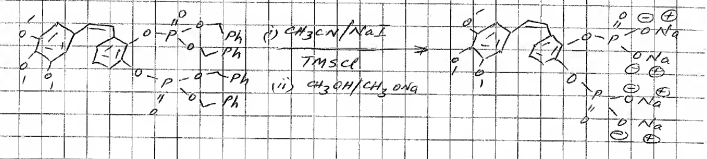
$^{13}C$ NMR PA-II-60

$$\text{yield} = \frac{0.71}{822.77} = .86 \text{ mmoles}$$

$$\% = \frac{0.86}{1.65} \times 100 = 52.29\%$$

# TETRASODIUM – DIPHOSPHATE

07/09/02

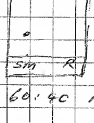



| MF | SM | NaI | TMSCl | $Na_2S_2O_3 \cdot 5H_2O$ | $CH_3ONa$ 25% | $CH_3CN$ | $CH_3OH$ |
|---|---|---|---|---|---|---|---|
| MW | 822 ~~822~~ | 149.89 | 108.64 | 248 | 54.02 | 9.5ml | |
| WT(g) | 0.71 | 0.52 | 0.37 (0.45ml) | 1 ml | 0.19 (0.8ml) | | |
| mmoles | 0.86 | 3.44 | 3.44 | | 3.44 | | |
| Ratio | 1 eq | 4 eq | 4 eq | 1% | 4 eq | | |

PROCEDURE: Raj Petit Antineoplastic agents 429 pg 207.

1. The phosphate was put under Ar.
2. $CH_3CN$ was added to it followed by NaI
3. The mixture was stirred for 2 mins, then chlorotrimethylsilane (distilled using $CaH_2$) was added dropwise.
4. 30 min later TLC was done to ensure that the SM was used up.

TLC




60:40 hexane : EtOAc

5. Reaction was terminated by addition 1% $Na_2S_2O_3$ ...

7. The mixture was dissolved in $H_2O$ - $CH_2Cl_2$
8. The $CH_2Cl_2$ layer was washed with $H_2O$ three times
9. The aqueous layer was concentrated using to form azeotrope
10. The residue was dried on vacuum pump overnight
11. The dry mixture (looked like foam and was dark Brownish in colour) was dissolved in $CH_3OH$, then $CH_3ONa$ was added and the solution was stirred for 6 hours

RECRYSTALLISATION 07/12/02

Tried recrystallizing using $H_2O$ - Ethanol
$H_2O$ - methanol
$H_2O$ - acetone
did not work.

Separated 40mg using prep TLC (70 : 30 water isopropanol)
Got 10 mg of the trans isomer
Separated 5 fractions by prep TLC

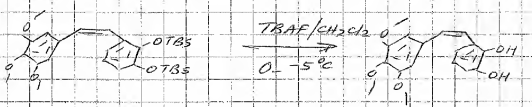
SEPARATION USING C-18 COLUMN 07/15/02

Tried separation using $CH_3OH$ : $H_2O$ : $CH_3CN$ system (Rano-3)
55 : 10 : 35
using C18 column first ran methanol then it (least polar)
The compound came out as a mixture.

Tried separation on prep TLC. It was a disaster.

# DEPROTECTION USING TBAF

07/30/01

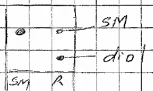



| | | | |
|---|---|---|---|
| MF | SM | TBAF in 1M THF | $CH_2Cl_2$ (dry) solvent |
| MW | 530.84 | 261.47 | |
| Ratio | 1 eq | 2.5 eq | |
| wt (g) | 3.8375 | 4.73 (18.1 ml) | |
| mmoles | 7.24 | 18.1 | |

PROCEDURE

1. The compound was put under Ar and dissolved in $CH_2Cl_2$
2. It was cooled to -5°C by adding common salt to ice bath
3. TBAF was added and TLC done after 15 mins.

TLC




70:30 hexane: EtOAc

4. Reaction was continued for 50 mins till all the SM was used up

TLC


70:30 hexane: EtOAc

5. The reaction was quenched with water & extracted the aqueous layer with $CH_2Cl_2$ twice.

6. The combined organic layers were dried over $Na_2SO_4$ anhydrous, filtered and rotavaped.

7. The dark brown colour oily crude was purified by column chromatography.

COLUMN CHROMATOGRAPHY.

The compound was purified by flash column chromatography using hexane: EtOAc 60:40 to yield 2.05g of diol

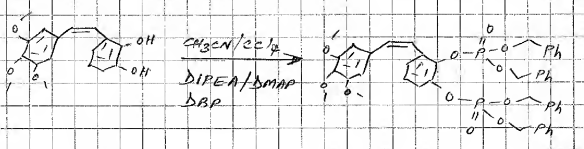
$^1H$- NMR PA-11-81

$$\text{yield \%} = \frac{2.05}{302.32} = 6.78 \text{ mmoles}$$

$$\frac{6.78}{7.24} \times 100 = 93.65\%$$

# DIBENZYL PHOSPHORYLATION

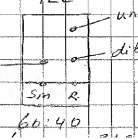
08/01/02




| | MF | SM | $CCl_4$ | DIPEA | DMAP | DBP | $CH_3CN$ | $KH_2PO_4$ 0.5M |
|---|---|---|---|---|---|---|---|---|
| | | 302.32 | | | | | | |
| MW | | 0.86 | 153.82 | 129.24 | 122.17 | 262.25 | | 136.09 |
| wt(g) | | 0.86 | 4.46 (2.8ml) | 1.57 (2.2ml) | 0.07 | 2.2 (1.85ml) | 17ml | |
| Ratio | | 1eq | 10eq | 4.2eq | 0.2eq | 2.9eq | | |
| mmoles | | 2.85 | 28.5 | 12.2 | 0.57 | 8.3 | | |

PROCEDURE: Ref GR Pedit, Anti-Cancer Drug Design (2000), 15, 203-216

1. The diphenol was put under Ar.
2. It was cooled to -20°C. Then $CCl_4$ was added and stirred for 10 min.
3. DIPEA and DMAP were then added.
4. After stirring for 1 min dibenzylphosphite was added and the temperature maintained below -20°C
5. After 45 min, TLC was performed.



6. The dibenzylphosphorylated compound appears at almost the same Rf as diol (water carefully).
7. The reaction was quenched with 0.5 M $KH_2PO_4$ and the mixture was allowed to come to r.t.
8. The aqueous layer was extracted with EtOAc four times, washed with brine, then with $H_2O$ and dried using $Na_2SO_4$ anhydrous.
9. It was filtered and concentrated.

COLUMN CHROMATOGRAPHY 08/02/02

The compound was loaded on column (wet loading) and flash column chromatography was performed using 3:2 hexane - ethyl acetate to afford 1.73 g of a colourless oil.

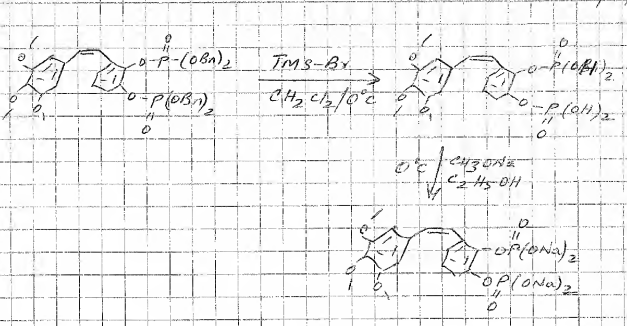
$^1H$ NMR PA-11-82

$^{31}P$ - NMR PA-11-83

$$\text{yield\%} = \frac{1.73}{822.77} = 2.10 \text{ mmoles}$$

$$\frac{2.10}{2.85} = 73.77\%$$

TETRASODIUM DIPHOSPHATE 08/03/02




PROCEDURE: Ref G R Pettit et all Anti Cancer Drug Design (2001) 16, 185-193

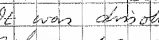
| | | | | | |
|---|---|---|---|---|---|
| MF. | SM | TMSBr | $CH_2Cl_2$ | $C_2H_5OH$ | $CH_3ONa$ |
| MW | 822 | 153.10 | | | 54.02 |
| wt(g) | 0.12 | 0.089(0.08ml) | 1.1ml | 2.2ml | 0.032 |
| mmoles | 0.146 | 0.583 | | | 0.583 |
| Ratio | 1eq | 4eq | | | 4eq |

$Na_2S_2O_{3(aq)}$ 10% → 1.1ml

PROCEDURE:

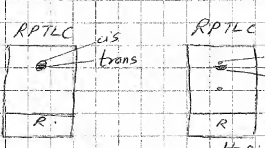
1. The tetra benzyl ester was put under Ar
2. It was dissolved in DCM at 0°C & bromo trimethyl silane was added.
3. After stirring for 15 min, TLC was done

TLC



fount quickly disappear (dibenzyl bromide)

4. The reaction was quenched with 10% $Na_2S_2O_3$ (aq.) after 25 min.




5. Isomerization had already taken place with a greater percentage going to trans and there was minor formation of cis.

6. The solvent aqueous layer was removed with a disposable pipette. It was extracted with EtOAc thrice. The combined organic layers were rotavaped and then dried on the vacuum pump. It took very long to dry even after 12 hours, it wasn't looking very dry.

7. It was then put under Ar, maintained at 0°C and quenched in $C_2H_5OH$.

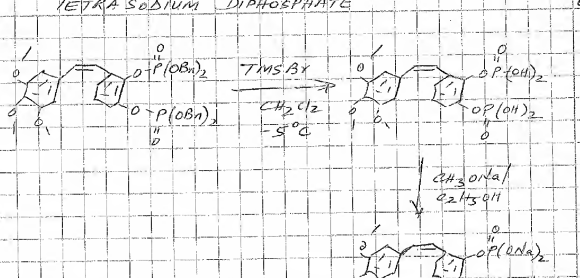
8. Sodium methoxide was quickly added and stirred for 30 min. Light yellow colour precipitate was obtained which was rotavaped.

9. It was triturated with ether, turned dark brown. TLC showed greater formation of trans.


10. RECRYSTALLIZATION from water, acetone was attempted but failed.

# TETRASODIUM DIPHOSPHATE

08/05/02

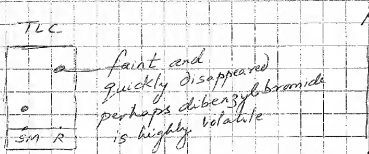



PROCEDURE: Ref G.R Pathi et all Anti Cancer Drug Design (2001) 16 pg 185-193

| SME | SM | TMSBr | $CH_2Cl_2$ | $CH_3ONa$ | $C_2H_5OH$ | $Na_2S_2O_3$ 1% + $CH_3COOH$ |
|---|---|---|---|---|---|---|
| MW | 822 | 153.10 | | 54.02 | | |
| Wt (g) | 0.100 | 0.075 (0.9ml) | | 0.026 | 1.8ml | 0.9ml |
| mmoles | 0.12 | 0.486 | | 0.486 | | |
| Ratio | 1eq | 4eq | | 4eq | | |

PROCEDURE: Ref GR Pathi et all Anti Cancer Drug Design (2001) 16, 185-193

1. To a stirred solution of tetrabenzyl ester in $CH_2Cl_2$ under Ar at 0°C - (-5°C), bromotrimethylsilane was added.
2. After stirring for 5 mins, TLC was done




60:40
Hexane: EtOAc

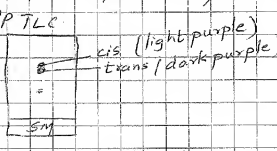
$H_2O$: $CH_3CN$
70: 30

$H_2O$: Isopropanol
70: 30

3 However the reaction was quenched with 1% $Na_2S_2O_3$ w/ $CH_3COOH$ (Note no water was used) only after 15 min on the RP TLC plates took long to develop

4 The solution was rotavaped using Toluene azeotrope & then $CH_2Cl_2$

5 ~~A~~ TLC was performed after rotavaping off the solvent




70:30 Water: Isopropanol

6 Perhaps the isomerization took place after 5 min

7 The compound (crude) was dried light yellow mixed with brown (mustard colour) on the vacuum pump for 6 hours It dried and was like a foam

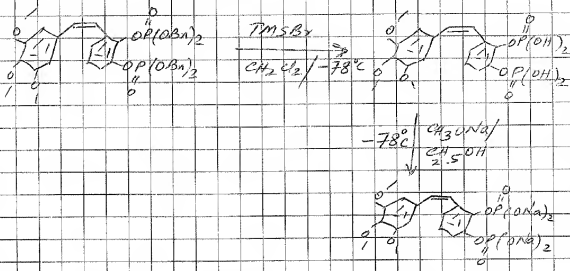
8 The dried crude was put under Ar, dissolved in $C_2H_5OH$ at 0°C.

9 $NaOCH_3$ was quickly added and stirred for 30 mins The compound was taken out, it was white in colour and rotavaped.

10 It was triturated with anhydrous diethyl ether

# TETRASODIUM DIPHOSPHATE

08/07/02




| MF | S/M | TMSBr | $CH_2Cl_2$ | $CH_3ONa$ | $C_2H_5OH$ | $Na_2S_2O_3$ (aq) 10% |
|---|---|---|---|---|---|---|
| MW | 822 | 153.10 | | 54.02 | | |
| Wt(g) | 0.13 | 0.098 | 1.2 ml | 0.035 | 2.4 ml | 1.2 ml |
| mmoles | 0.16 | 0.64 | | 0.64 | | |
| Ratio | 1 eq | 4 eq | | 4 eq | | |

PROCEDURE Ref GR Pathak et all, Antineoplastic Agents 460
Anti-Cancer Drug Design (2001), 16, 185-193

1. The tetrabenzyl ester was put under Ar
2. Temp was -78°C. It was dissolved in Dichloro-methane
3. TMSBr was added & temp maintained at -78°C
4. After stirring for 5 min, 15 min, 30 min, 45 min. TLC was done.

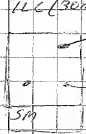
TLC (5 min)

very light

TLC (15 min)


60:40
hexane: EtOAc

TLC (30 min)




60:40
hexane: EtOAc

TLC (45 min)


60:40
hexane: EtOAc

5. After stirring for 45 min the rxn was quenched with 10% $Na_2S_2O_3$ (aq) and stirred for 5 more min. It looked like a creamy ppt mixed with an oily layer.

6. The creamy layer was removed using a disposable pipette into a tt. It was extracted with EtOAc thrice.

7. The combined organic layers were rotavaped finally a little toluene (was added and rotavaped.

8. A colourless oily liquid (phosphonic acid) intermediate was obtained which was dried on the vacuum pump.

RP TLC


50:50
water: $CH_3CN$